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EFFECT OF A PROPRIETARY HERBAL MEDICINE ON THE RELIEF OF CHRONIC ARTHRITIC PAIN: A DOUBLE-BLIND STUDY

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SUMMARY

Eighty-two subjects with chronic arthritic pain were randomly assigned for 2 months without cross-over to either Reumalex, a licenced over-the-counter (OTC) herbal medicine, or a placebo. Entry characteristics were determined by a previous survey of arthritic customers at pharmacy and healthfood shop outlets. The AIMS2 questionnaire was completed at monthly intervals throughout and for 2 months prior to the trial, and a modified Ritchie Index provided clinical scores. Subjects also completed diary recordings of their use of self-prescribed analgesics and events they considered significant. There was a small but statistically significant improvement in pain symptoms, less so in sufferers from osteoarthritis. There were no other significant changes in any other measures nor in the use of other self-prescribed analgesics. There were few side-effects noted. It is concluded that Reumalex has a mild analgesic effect in chronic arthritis at a level appropriate to self-medication.

KEY WORDS: Osteoarthritis, Rheumatoid arthritis, Self-medication, Herbal remedies, Health assessment questionnaires, Joint indices.

THERE are many products available for sale at pharmacy and retail outlets which arthritic patients can prescribe for themselves. Some are prescribed drug to over-the-counter (OTC) 'switches', i.e. they are proprietary versions of original ethical drugs which have gone through conventional medical routes of acceptance (e.g. ibuprofen). Some, like the fish oils, arise out of very long popular traditions and their use has been supported by clinical studies or the modern identification within them of active anti-inflammatory agents; others are supplied with little or no rationale.

The use of natural remedies, in particular, is increasing markedly [1], a trend given new impetus by the decision of Boots the Chemists to promote herbal and homoeopathic preparations. The physician could justifiably ask that more information be made available as to whether or how these remedies might work and what impact they might have on the use of prescribed drugs.

Reumalex (Gerard House Ltd, 375 Capability Green, Luton) is a licensed herbal medicine that has for many years been sold OTC for the alleviation of arthritic pain. It was considered most appropriate to study its effects in context, i.e. on those most likely to use such remedies. A pilot survey among arthritic customers at pharmacies and healthfood shops suggested that most users had long-established and generally stable symptoms.

The aim of this double-blind controlled clinical trial was to measure the effect of Reumalex on the symptomatic relief of chronic joint pain compared with placebo on the basis of three observations: (1) normalized arthritis pain scores from self-administered AIMS2 questionnaires completed by each subject each month of a 2 month trial as well as over 2 months previously; (2) clinical application of a modified Ritchie Index at the start and completion of the trial; (3) diary reports of concomitant use of self-prescribed analgesics.

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PATIENTS AND METHODS

Individuals with arthritic pain were recruited from Exeter and the surrounding areas, through pharmacy and health store outlets, and by articles in newspapers and magazines. The AIMS2 is a revised and expanded version of the Arthritis Impact Measurement Scales Health Status Questionnaire which has established validity, reliability and sensitivity in monitoring changes in therapeutic interventions [2, 3]. Applicants were initially vetted with the AIMS2 questionnaire, and their family doctors were then contacted and asked to comment on their suitability for admission into the trial. Those who satisfied all stages of acceptance completed a total of three AIMS2 questionnaires over the 2 months prior to the trial to establish baseline variability, as well as a consent form and a diary. The condition of those accepted was then clinically assessed by a rheumatologist (RKJ) and the diagnosis was recorded, with levels of disability, joint damage, pain and wider distress also noted. While still under supervision, a metrologist applied a modified Ritchie score [4, 5]. Subjects were then assigned, by accession to pre-set lists of allocations randomized for equalization in every 10, and after stratification by clinical condition, into two matched groups. All involved in the study were blind to the allocations. Subjects in each group received medication for 2 months, one group receiving the test compound, the second a placebo. Because of the strong likelihood of carry-over effects, there was no cross-over of treatment. An AIMS2

questionnaire was completed at the end of each month of the study (making five readings in all), as well as a daily diary throughout. At the end of the 2 months, the subjects reported back for a second clinical appraisal using the Ritchie score.

To satisfy inclusion criteria (determined from the previous survey of OTC users), subjects had to be ambulant, with either osteoarthritis (OA) or rheumatoid arthritis (RA) and scoring pain scores on the entry AIMS2 questionnaire of $\geqslant 3$. The main exclusion criterion was the concurrent prescription of salicylate and other anti-inflammatory medication or constant use of prescribed analgesics. Others were joint pain from other pathologies, severe cardiovascular disease, prescription of antithrombotics, insulin and digoxin, known salicylate sensitivity, mental incapacity, liver, kidney or neurological disease, malignant disease, and pregnancy and lactation.

Subjects were permitted to maintain their current levels of self-prescribed medication, including analgesics, throughout the trial, but were asked not to start new brands. They were asked to record all use of analgesics, other remedies and supplements in their diary. Medical practitioners were asked to keep the trial in mind, particularly in that the prescription of anti-inflammatory drugs would lead to withdrawal. Ethical review was provided by the Exeter Medical Research Ethics Committee.

Test remedy

The test product is a mixture of five herbs, marketed as Reumalex, with a reviewed full product licence for sale direct to the public as a 'traditional herbal remedy for the symptomatic relief of rheumatic aches and pains, fibrositis, lumbago, backache and stiffness'. Two white bi-convex sugar-coated tablets are taken at a time. Each tablet contains: Pulv White Willow Bark BHP, 100 mg; Pulv Guaiacum Resin BHP, 40 mg; Pulv Black Cohosh BHP, 35 mg; Pulv Ext Sarsaparilla 4:1, 25 mg; Pulv Ext Poplar Bark 7:1, 17 mg. This is a traditional herbal formulation for arthritic conditions and contains modest levels of salicylates (primarily as salicortin and salicin in the willow and poplar barks) perhaps equivalent to 20–40 mg salicylic acid in a two-tablet dose [6, 7]. There are, moreover, a wide range of other established anti-inflammatory constituents among the ingredients, including other (salicylate-like) phenolic glycosides, lignans, resin acids, triterpenes and steroidal saponins [8–11], and there is also evidence that after consumption of willow bark salicylate levels in the blood rise more slowly [12] and remain raised for longer than after the consumption of the equivalent dose of salicylate itself [13]. Between them, the ingredients cover a range of traditional indications and there is pharmacological evidence among their constituents of additional antiviral [14], antitubercular [15], antidiabetic [16], vasodilatory [17], antispasmodic, sedative and hypotensive activity [18], as well as specific binding to oestrogen receptors [19]. All these latter activities are likely to be at low levels at the dosage provided. Toxicological reports for the plant constituents of the test remedy refer only to the effects of salicylates (and there are recent references to renal papillary necrosis and haemolysis at high doses of salicin [20, 21]), but the test remedy provides its ingredients at levels well below any such activity. It is, however, possible that individuals with salicylate sensitivity might be liable to reactions, and this was an exclusion criterion. Subjects were asked to record any effects, both positive and negative, in their diaries. They were additionally provided with a contact number for any enquiries.

An identical placebo tablet was produced containing calcium phosphate.

The early involvement of the subjects in returning completed forms and then taking the trouble to attend for clinical assessment markedly reduced the drop-out rate expected for distance trials. Subjects were issued with more tablets than necessary for each month's treatment. They were asked to return all containers on the final clinical assessment for counting.

RESULTS

Of over 300 initial recruits, 82 satisfied all inclusion and exclusion criteria, and completed all stages of the pre-trial observations; a total of 72 subjects completed the trial in all its stages and within the terms of compliance. Analysis of standardized AIMS2 scores before treatment showed that there were no significant differences between treatment and placebo groups in any scale or measure. As there were good baseline data, it was possible to measure change on each scale by taking the sum of each subject's paired differences (score at end of treatment minus score at start).

The subjects were, as expected, relatively elderly with long-term arthritis (mean age 62.21 yr, S.D. 12.05; mean chronicity 10.8 yr, S.D. 8.76). The most obvious finding was the stability of their arthritic symptoms as measured by the AIMS2 questionnaire, both before and during the trial. This was an aim of recruitment and followed the results of the pilot survey of users of OTC remedies for arthritis. Thus, in Table I, mean disability scores (with clinical improvement judged as a global reduction in scoring across all scale items from 0 to 10) for mobility, walking and bending, hand and finger function, and arm function were low at outset and stayed almost unchanged throughout with no significant differences between placebo and treatment groups. A similar pattern held for self-care tasks, household tasks, social activity, and support from family and friends scores. Tension levels scored slightly higher, and there was a modest improvement in scores for both placebo and treatment groups throughout the study, but this change was not statistically significant. There was a greater, but also not statistically significant, improvement in mood scores among those taking Reumalex than placebo; interestingly, individual changed scores were not well correlated with changed pain scores (Pearson's r correlation coefficient = 0.27).

In the AIMS2 questionnaire, the Arthritis Pain scale was chosen as the key measure. After pursuing calculations in Table II, it was possible to accept the

TABLE I
Analysis of paired differences for functional disability and affect scores in the Reumalex and placebo groups

	Mobility	Walking and bending	Hand and finger function	Arm function	Level of tension	Mood
Mean Reumalex paired differences	0.09	0.11	0.30	0.01	−0.14	−0.54
S.D. Reumalex paired differences	1.02	1.22	1.51	0.93	1.73	2.24
Mean placebo paired differences	0.08	−0.21	0.06	−0.12	−0.08	0.15
S.D. placebo paired differences	0.70	2.15	1.04	0.53	1.67	1.98
Difference in paired differences	0.01	0.32	0.24	0.13	−0.06	−0.38
S.E.	0.20	0.40	0.30	0.18	0.39	0.30
z	0.05	0.81	0.80	0.75	−0.15	−1.27
P	0.9601	0.4179	0.4237	0.5823	0.8808	0.2041
95% confidence interval	−0.39	−0.46	−0.35	−0.21	−0.82	−0.97
	0.41	1.10	0.83	0.48	0.71	0.21

hypothesis that there was a difference in pain scores in those taking Reumalex compared with those on placebo ($P < 0.05$).

To take advantage of the 2 months baseline period, a second calculation was made averaging scores over the 2 months prior to treatment and deducting this from the end of treatment score (the scores asterisked in Table II). Here, the result was also a significant relative improvement in the treatment group ($P < 0.05$).

The clinical assessment, applying the modified Ritchie score, was used as a second measure with changes in global scoring at the start and end of treatment. Again, there was a relative improvement among the treatment group and the result was significant ($P < 0.05$).

When equivalent calculations were conducted for the larger subgroup of subjects ($n = 51$) diagnosed with OA, there was a slightly smaller but still statistically significant treatment effect as measured by the AIMS2 score ($P < 0.05$), stronger when baseline scores were averaged over the 2 month trial period ($P < 0.05$), but with the Ritchie score there was no difference ($P > 0.5$).

There was widespread complaint of the effect on symptoms of the particularly cold, damp and windy weather at the end of the trial. This was reflected in individual scores: eight in the Reumalex group and 15 in the placebo group recorded worse AIMS2 pain scores (those recording worse Ritchie scores numbered 13 and 12, respectively). Against this adverse gradient, relatively few subjects recorded substantial changes in pain relief: eight subjects taking Reumalex recorded more than a two-point improvement on the 10-point scale (compared to five in the placebo group), while eight Reumalex subjects recorded more than a five-point improvement in the Ritchie score (compared with two in the placebo group).

The authors of the AIMS2 questionnaire suggest a

TABLE II
AIMS2 and Ritchie scores for treatment and placebo groups for the study as a whole and for the osteoarthritic subgroup; diary scores for the group as a whole; paired difference calculations and standardization with *P* values and confidence intervals throughout

	AIMS2 pain scores 1	AIMS2 pain scores 2*	Modified Ritchie scores	AIMS2 pain scores OA group 1	AIMS2 pain scores OA group 2*	Modified Ritchie scores OA group	Diary scores of analgesic use
Mean Reumalex scores at outset ($n = 35$) (OA: $n = 25$)	5.01	5.43	11.24	4.71	5.16	10.13	0.65
S.D. Reumalex scores at outset	1.55	1.56	9.95	1.37	1.43	9.00	0.75
Mean placebo scores at outset ($n = 37$) (OA: $n = 27$)	4.68	4.99	10.30	4.58	4.88	6.96	1.04
S.D. placebo scores at outset	1.78	1.68	12.76	1.87	1.64	6.73	1.33
Mean Reumalex scores at end	4.24	4.24	9.88	3.94	3.94	9.92	0.71
S.D. Reumalex scores at end	1.84	1.84	8.32	1.66	1.66	8.18	0.84
Mean placebo scores at end	4.73	4.73	11.53	4.70	4.70	7.42	0.78
S.D. placebo scores at end	2.52	2.52	13.98	2.43	2.43	6.79	1.20
Mean Reumalex paired differences	−0.77	−1.14	−1.36	−0.77	−1.22	−0.21	0.02
S.D. Reumalex paired differences	1.51	1.49	4.66	1.65	1.64	4.66	0.63
Mean placebo paired differences	−0.05	−0.26	0.91	0.12	−0.18	0.38	−0.27
S.D. placebo paired differences	1.63	1.77	3.73	1.41	1.69	3.73	1.61
Difference in paired differences	0.83	0.88	2.28	0.89	1.04	0.58	−0.29
S.E.	0.38	0.39	1.05	0.44	0.48	1.23	0.30
z	2.20	2.27	2.17	2.03	−2.18	0.47	0.95
P	0.0278	0.0232	0.0300	0.0424	0.0293	0.6384	0.3410
95% confidence interval	−1.56	−1.63	−4.33	−1.75	−1.97	−2.99	−0.31
	−1.09	−0.12	−0.22	−0.03	−0.11	1.82	0.88

*Pain score at outset is made up of the mean of two scores: at the start of the trial and 2 months previously.

calculation for effect size analysis, to estimate the clinical significance of any observed change. This entails dividing the difference between treatment and placebo groups by their pooled S.D. values. The result in this case is that the relative improvement in the Reumalex group constituted just over a half (0.53) of 1 S.D. of the change for the sample as a whole.

Reported changes in parallel analgesic consumption were compared with baseline levels recorded in diaries in the pre-treatment phase. Each single dose of OTC analgesic (whatever the formulation) was scored as one and a continuous record was kept over the observation period. A mean daily score was achieved for each subject by averaging unit dose rates for each month (this averaged about 0.6 of a unit dose per day). The mean daily score was compared for the second month of treatment with that for the month prior to treatment and a score difference resulted. After respective standard scores were calculated, it was clearly not possible to reject the null hypothesis that there was no difference in analgesic consumption in the two groups ($P > 0.1$).

The numbers withdrawing from the trial because of adverse effects were small: four each in the treatment and placebo groups. Of the former, one complained of dyspeptic symptoms within a day of starting treatment, one had diarrhoea in the second month, one had severe headaches in the second month and was withdrawn as a precautionary measure by her family doctor; the fourth withdrew for reasons unrelated to the intervention. Of the placebo group, one withdrew immediately with headaches and digestive upsets, and three in the second month with, respectively, angina, anxiety and stomach cramps. Two others in the treatment group and three in the placebo group reported exacerbation of their arthritis, but completed the study.

DISCUSSION

This study was an assessment of the permitted claims for symptomatic analgesia for a medicine licensed under the terms of the Medicines Act 1968 and relevant EC Directives, with efficacy claims substantiated by bibliographic evidence and traditional use. There was no attempt to demonstrate any curative effect of the herbal treatment on any particular arthritic pathology.

The earlier survey of potential users of OTC medicines had suggested that they were likely to have chronic stable arthritic conditions, having used a range of prescription and other medications in the past, with moderate disability but with pain as the principal complaint. Recruitment was targeted at these patients, with the major exclusion criterion, for operational reasons, being the prescription of anti-inflammatory medication. Clinical assessment of the study sample indicated that the main arthritic complaint in the relevant population was degenerative OA, and that even those diagnosed with RA and other inflammatory arthropathies were unlikely to suffer acute exacerbations. Stability of symptoms were thus expected and this was confirmed by screening over the 2 months before the trial.

Symptom movement during the trial was also minimal, there being for example almost no perceptible placebo effect in any measure apart from those of tension and mood. One factor that might have led to this lack of benefit was the relatively unpleasant climatic conditions prevailing at the end of the study.

Only in the pain scales were such benefits recorded and on analysis of paired differences these were indeed shown to be statistically significant. Improvements were nevertheless minor, and in the 2 months of observation the already low mean mobility and function scores were unaffected. There are doubts about the ability of any questionnaire to reflect changes at the low end of the distress scale, and it would be statistically imprudent to attempt correlation studies at this level.

Those with OA showed less improvements on the questionnaire scales, and the articular palpation scale did not detect significant benefits in this group. Although a modified version of the Ritchie Index was applied to pick up pain of OA, it was obvious (from the relatively high number of distal joints palpated) that it remained more sensitive to changes in those with rheumatoid conditions and was unduly influenced by relatively minor fluctuations in the latter group.

The lack of sensitive measures of change in low-grade OA was apparent in this study. It is possible that the disproportionate effect on outcome of the minority RA group may simply reflect the relative sensitivity of this condition to available measures. Nevertheless, this study does suggest the possibility of an anti-inflammatory effect for the herbs and the potential of a further study on RA patients using ESR and other specific clinical markers.

There was no significant difference in the consumption of other analgesics. This showed that the treatment effect was not sufficient to change what in many cases may have been habitual use. The climatic adversities mentioned earlier may also have influenced the findings.

There was an interesting relative improvement in mood scores in those taking the herbal treatment and this was not correlated to improvements in pain scores. Although the changes were not significant, given the range of traditional uses to which some of the herbs in the mixture have been used, this is an intriguing pointer to other potential activity.

The herbal formula examined here has a rational basis for its action. Willow bark was the traditional treatment for inflammatory diseases that led early science to the discovery of the salicylates and aspirin. Poplar bark has a similar chemical profile and reputation; black cohosh, guaiacum and sarsaparilla all have strong reputations in treating rheumatic conditions in North American Indian and settler traditions. All the ingredients in this formulation are in low doses, as is appropriate for OTC treatments, so a dramatic effect was not expected. There were few adverse effects that were directly due to taking the

treatment. The effect observed will not transform the treatment of severe arthritic disease, and may even be masked by anti-inflammatory prescriptions, but it reassures the physician and regulator that self-prescribers with relatively low-grade stable conditions who wish to try the medicine for a few weeks are unlikely to be interfering with prescribed treatment.

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REFERENCES

1. *Complementary medicines*. London: MINTEL Market Intelligence, May 1995.
2. Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE. AIMS2. The content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire. *Arthritis Rheum* 1992;**35:**1–10.
3. McDowell I, Newell C. *Measuring health: a guide to rating scales and questionnaires*. New York: Oxford University Press, 1987:271–7.
4. Ritchie DM, Boyle JA, McInnes JM *et al*. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med NS* 1968;**37:**393–406.
5. Doyle DV, Dieppe PA, Scott J, Huskisson EC. An articular index for the assessment of osteoarthritis. *Ann Rheum Dis* 1981;**40:**75–8.
6. Steele JW, Bolan M, Audette RC. Phytochemistry of the Salicaceae. II. The effect of extraction procedures on the apparent free phenolic glycoside content of Salix species. *J Chromatogr* 1969;**40:**370–6.
7. Lin M, Li SZ. Studies on the chemical constituents of *Populus tomentosa* carr. *Yao Hsueh Hsueh Pao* 1993;**28:**437–41.
8. Bradley P (ed.) *British herbal compendium*, Vol. I. Bournemouth: British Herbal Medicine Association, 1992.
9. Ageel AM, Mossa JS, al-Yahya MA, al-Said MS, Tariq M. Experimental studies on antirheumatic crude drugs used in Saudi traditional medicine. *Drugs Exp Clin Res* 1989;**15:**369–72.
10. *British herbal pharmacopoeia*. Bournemouth: British Herbal Medicine Association, 1983.
11. Duwiejua M, Zeitlin IJ, Waterman PG, Gray AI. Anti-inflammatory activity of *Polygonum bistorta*, *Guaiacum officinale* and *Hamamelis virginiana* in rats. *J Pharm Pharmacol* 1994;**46:**286–90.
12. Meier B, Liebi M. Salicinhaltige pflanzliche Arzneimittel. Überlegungen zu Wirksamkeit und Unbedenklichkeit. *Z Phytother* 1990;**11:**50–8.
13. Fotsch G, Pfeifer S. Comparative study of serum levels of salicylic acid after oral administration of salicin and sodium salicylate in rats. *Pharmazie* 1990;**45:**535–6.
14. Van Hoof L, Totte J, Corthout J *et al*. Plant antiviral agents, VI. Isolation of antiviral phenolic glucosides from Populus cultivar Beaupre by droplet counter-current chromatography. *J Nat Prod* 1989;**52:**875–8.
15. Grange JM, Davey RW. Detection of antituberculous activity in plant extracts. *J Appl Bacteriol* 1990;**68:** 587–91.
16. Roman-Ramos R, Lara-Lemus A, Alarcon-Aguilar F, Flores-Saenz JL. Hypoglycemic activity of some antidiabetic plants. *Arch Med Res* 1992;**23:**105–9.
17. Rauwald HW, Brehm O. Screening of nine vasoactive medicinal plants for their possible calcium antagonistic activity. *Phytother Res* 1994;**8:**135–40.
18. Williamson EM, Evans FJ. *Potters new cyclopaedia of botanical drugs and preparations*. Saffron Walden: C. W. Daniel Co., 1988.
19. Jarry H, Harnischfeger G, Düker E. Studies on the endocrine effects of the contents of *Cimicifuga racemosa*. 2. *In vitro* binding of compounds to estrogen receptors. *Planta Med* 1985;**51:**316–9.
20. Schwarz A. Beethoven's renal disease based on his autopsy: a case of papillary necrosis. *Am J Kidney Dis* 1993;**21:**643–52.
21. Baker S, Thomas PS. Herbal medicine precipitating massive haemolysis [Letter]. *Lancet* 1987;**i:**1039–40.